

PCT

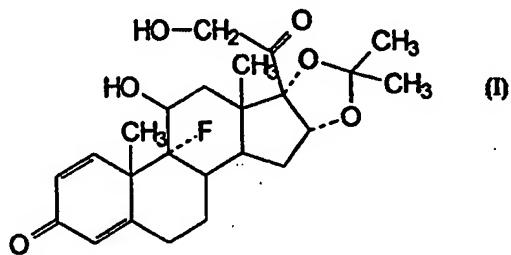
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(54) Title: TREATMENT OF AGE-RELATED MACULAR DEGENERATION



(57) Abstract

The present invention relates to the treatment of inflammatory response in the macula of the eye by use of a depot injection into the vitreous humour of a suitable anti-inflammatory agent. In particular, this invention relates to the use of triamcinolone acetonide (I) which is in crystalline form and is sparingly soluble in the vitreous of the eye, and which does not leave any vision impairing residue in the eye, for the treatment of age-related macular degeneration.

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Treatment of Age Related Macular Degeneration

Technical Field

The present invention relates to the treatment of inflammatory response in the macula of the eye^{1,2,3,4,5,6} by use of a depot injection into the vitreous humour of a suitable anti-inflammatory agent. In particular it relates to the treatment of age-related macular degeneration and more particularly relates to the treatment of the end stage of this condition with anti-inflammatory steroids. This end stage previously has been presumed to be untreatable.

Background Art

10 The major cause of registerable blindness in developed countries is due to the condition known as age-related macular degeneration⁷. In this condition, the macula which is a minute area in the centre of the retina is damaged. The macula occupies a total area of less than 1mm². This area is especially adapted for acute and detailed vision. In the central portion of the macula, known as the fovea (which is 0.4mm in diameter) the 15 blood vessels, and other cells are displaced to the side, allowing light to fall onto the photosensitive layer. This is in contrast to other parts of the retina where light has to pass through several layers of tissue before arriving at the photosensitive layer.

15 The condition itself is conveniently divided into three stages. It may present as early stage macular degeneration. At least 20% of patients develop an active 20 neurovascular form.

One end stage of this condition is known as atrophic macular degeneration (AMD) while a second end stage is known as neovascular macular degeneration (NMD), which is caused when new blood vessels begin to grow under the retina, particularly the macula.

25 AMD is not treatable, whereas NMD in some cases may be relieved by laser treatment. However, a complication of laser treatment is actual loss of vision. In addition, laser treatment, where applicable, is not always a permanent cure since the blood vessels may begin to grow again.

30 The problem of macular degeneration is immense. It has been estimated that 25% of people 70 and over in the developed world will have the mild form of the condition while 1 in 10 have severe symptoms and 1 in 100 progress to complete blindness.

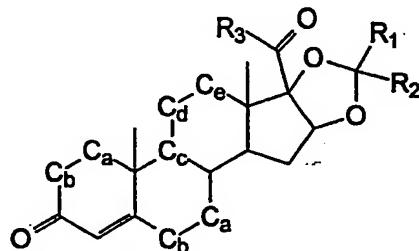
The present inventors have recently demonstrated that intravitreal injection of an anti-inflammatory steroid in depot form substantially arrests and/or reverses AMD and NMD.

35 It has been shown^{8,9} that intravitreal administration of anti-inflammatory steroids inhibits vascular proliferation in the eye. The inventors have shown^{1,2,3,4,5} in human patients that AMD is promoted by choroidally derived inflammatory cells. The inventors recently described resident immunocompetent cells⁵ in the neural retina which would be subject to the influence of intravitreal anti-inflammatory steroids.

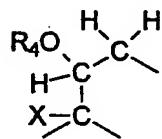
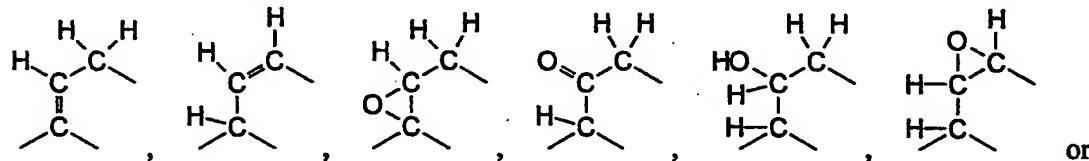
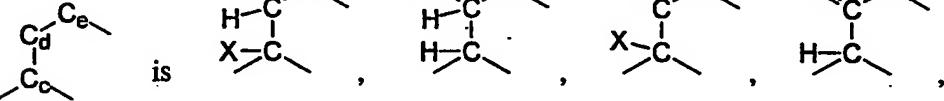
Disclosure Of The Invention

According to a first form of this invention there is provided a method for the treatment or prophylaxis of macular degeneration in a patient requiring said treatment or prophylaxis, comprising administering by intravitreal injection to said patient an effective amount in depot form of an anti-inflammatory steroid which is preferably sparingly soluble in the vitreous.

Preferred steroids include 11-substituted 16 α ,17 α -substituted methylenedioxy steroids of the formula

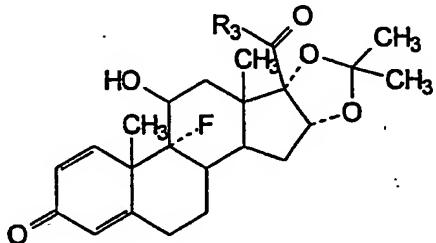


10 wherein



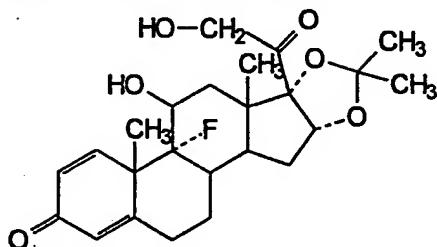
; R₁ and R₂ are hydrogen or alkyl; —C_a—C_b— is —CH₂—CH₂—, —CH₂—CH—, —CH=CH—, or —CH=C—; R₃ is methyl, hydroxymethyl or alkylcarbonyloxymethyl, methylaminoalkylenecarbonyloxymethyl, or phenylaminoalkylenecarbonyloxymethyl; R₄ is alkanoyl; and X is halogen.

More preferred are compounds of the formula



wherein R₃ is hydroxymethyl, phenylcarbonylaminoisopropylcarbonyloxymethyl, or 2,2-dimethylpropylcarbonyloxymethyl.

The preferred steroid is crystalline 9-fluoro-11,21-dihydroxy-16,17-[1-methylethylidinebis(oxy)]pregna-1,4-diene-3,20-dione:



This compound, also known by its generic name as triamcinolone acetonide is
5 suitably prepared by known methods^{10,11,12,13}.

The steroids are preferably crystalline and are administered in distilled water with a minimum of carriers or adjuvants. However, a depot pharmaceutical composition comprising an effective amount of said anti-inflammatory steroid together with a pharmaceutically and ophthalmologically acceptable carrier, diluent and/or excipient may
10 be used.

When triamcinolone acetonide is used, such a preparation may be made up by using Kenacort-A40 (registered trade mark) (Squibb) as the anti-inflammatory steroid. Suitable pharmaceutically acceptable salts of this compound may be used. For example, the acetate of triamcinolone acetonide may be used.

15 As the steroids suitable for use in this invention are sparingly soluble in the vitreous, crystalline forms are suitable for administration. The steroids may be formulated with carriers, diluents and/or excipients which are compatible with the vitreous and which do not leave any vision impairing residue in the eye.

The composition of the present invention is administered by intravitreal injection by
20 methods known in the art. For example, the eye is washed with a sterilising agent such as Betadine and the steroid is injected in distilled water with a fine gauge (eg. 27gauge) needle at a position in the eye such that the steroid crystals will settle to the posterior pole towards the ventral surface. It may also be necessary to prepare the eye for injection by application of positive pressure prior to injection. In some cases, paracentesis may be
25 necessary.

The steroid should be as concentrated as feasible to minimise the volume to be injected. The dosage of steroid may be between about 1mg and about 8mg. Typically,
30 4mg of steroid is deposited intravitreally and thus it is necessary to inject 0.1mL of Kenacort-A40 solution. This dosage range is applicable to each of the three following stages of macular degeneration, namely: early onset macular degeneration, atrophic macular degeneration (AMD) and neovascular macular degeneration (NMD).

The frequency of method of treatment of this invention is not more than 3 monthly.
In many cases, a single administration *per annum* may be sufficient.

35 The compositions of this invention may also be presented as a unit dose in a syringe ready for administration.

The method of the present invention may be practised alone or in conjunction with other therapy. Where laser treatment of the retina is indicated, steroid may be injected before or after the laser treatment. Other substances, for example antibiotics and anti-angiogenesis agents for example thalidomide, may be injected with the steroid.

- 5 In more than 50% of cases where AMD occurs in one eye, it will occur in the other eye within one year. Prophylactic administration of steroid into an unaffected eye may be useful in such cases.

Brief Description of Drawing

Figure 1 is a comparison between change in visual acuity in three groups of
10 patients.

Best Modes And Other Modes For Carrying Out The Invention

An effective amount of triamcinolone acetonide to arrest and/or reverse macular degeneration is administered by intravitreal injection when such a procedure is indicated.

The present invention will now be described with reference to the following
15 examples which should not be construed as limiting on the scope thereof.

Example 1

Kenacort-A40 (Squibb) (40mg/mL) as supplied is prepared for administration of 0.1mL.

Example 2

20 Six patients were injected with 0.1mL Kenacort-A40. The patients were monitored weekly by direct observation including colour vision, electrophysiological responses of the retina and dynamic studies of the retinal circulation using fluorescein angiography.

Example 3

25 The influence of intravitreal triamcinolone on microglial distributions in AMD: a case study

The source of the signals which initially provoke choroidal neovascularisation has not been defined, although immune mediation of neovascularisation by both choroidally derived leucocytes and retinal microglia remain significant possibilities. As part of a pilot study, one patient with subfoveal choroidal new vessels received intravitreal triamcinolone 30 in her left eye. Angiography showed that exudation decreased and vision improved. Unfortunately, the patient died within 6 weeks of the administration as a result of cardiovascular failure, but donated her eyes for histopathological examination. The immunohistopathological findings of this unique case study are summarised below.

Methods: Eyes were fixed in 2% paraformaldehyde for 24 hours at 4°C. The delay 35 between death and fixation of both eyes was 25 hours. Following fixation, the neural retina was separated from RPE (ie retinal pigment epithelium)/choroid portion which was postfixed and examined histopathologically in semithin sections. Primary monoclonal

antibodies (MHC class II & CD45) were applied to retinal wholemounts and detected using silver-toned immunogold.

The distributions and phenotypic characteristics of microglia in normal age-matched adult retinae, the treated and untreated retinae were compared.

5 Results: Both the treated and the untreated RPE/choroidal specimens showed similar early disciform lesions which were not obviously altered as a result of the steroid administration. Microglia were morphologically hypertrophic in the untreated retina while the number of microglia was not significantly increased, consistent with our earlier findings. However microglial morphology was less ramified and cell numbers were
10 significantly less in the treated retina.

Conclusions: Comparison of microglial numbers labelled with MHC class II and CD45 antibodies indicated that in addition to reduced cell numbers, triamcinolone administration effected reduced expression of MHC class II by microglia, but not vascular elements.

15

Example 4

Comparison between change in visual acuity in triamcinolone treatment and laser treatment

Figure 1 graphically illustrates a comparison between the change in visual acuity in a group of patients treated with triamcinolone, and a previous study involving a group of
20 patients treated with laser therapy and a group of patients in which no treatment was given (control group). The triamcinolone group was studied for 10 months. The two previously reported groups were studied for a period of 42 months.

The table on the following page sets out the results for the triamcinolone group.

It can be seen from the graph in Figure 1 that there was in fact an initial increase in
25 visual acuity in the triamcinolone group. The group treated with laser therapy suffered a decrease of 3 lines of visual acuity within 3 months. This then remained stable for a period of up to 42 months. The control group experienced less of an initial, decrease falling to 2 lines within 3 months. However, the control group steadily decreased over the period of study, reaching a decrease of 5 lines of visual acuity by 42 months.

Table

Patient No	Age/Sex:	Eye:	Visual Acuity				Disorder (Treated Eye Only)	Drusen
			0/12	1/12	3/12	6/12		
1.	80/F	Left	1	p5	p5	p5	p5	mCNV + occCNVs + HAEM + hEx + Oed
2.	82/M	Left	1	0	0	0	0	ICNV + fib + mHAEM + EBF + Oeb
3.	80/F	Right	9	p2	m2	m2	m6	sCNV + EBF + Pigdist + Oed
4.	78/F	Right	10	p2	0	m0.5	p3	sCNV + EBF + Pigdist + Oed
5.	84/M	Right	3	p1	p3	p4	p4	mCNV + occCNV + sHAEM + EBF + hEx
6.	78/F	Left	8.5	p1	p0.5	m1.5	m1.5	mCNV + Pigdist + EBF + Oed
7.	90/F	Left	0.5	0	0	p0.5	N	mCNV + EBF + sHAEM + hEx + Oed
8.	76/F	Left	8	m1	N	N	N	2(s+m)CNV + Haem
9.	80/F	Left	7	0	N	N	N	mCNV + fibr + serDet
Change			basis	p.1.1	p0.93	p0.78	p0.75	Many h

Lineage of the visual acuities

- 1 = 1/60 6 = 6/60 11 = 6/9 s = small (<1DA), m = medium (1-2DA)
 2 = 2/60 7 = 6/36 12 = 6/7.5 l = large (>2DA) occ = occult,
 3 = 3/60 8 = 6/24 13 = 6/6 fib = fibrosis, serDet = serous detachment
 4 = 4/60 9 = 6/18 14 = 6/5 hEx = hard exudates, EBF = elevated blocked fluorescence
 5 = 5/60 10 = 6/12 15 = 6/4 Pigdist = pigment disturbance

h = hard

s = soft

c = calcified

a = atrophic

Industrial Applicability

It should be clear that the methods of treatment of this invention will find wide use in the medical field.

The foregoing describes only some embodiments of the present invention and 5 modifications obvious to those skilled in the art can be made thereto without departing from the scope of the invention.

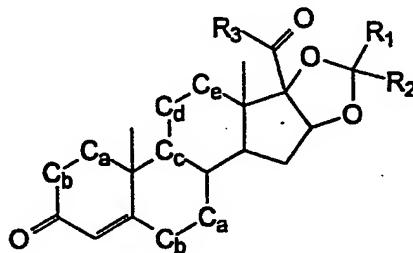
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- 12 US 2 990 401.
- 13 US 3 035 050.

Treatment of Age Related Macular Degeneration

Claims

1. Use of an anti-inflammatory steroid for the manufacture of a medicament for treating macular degeneration by intravitreal injection of said steroid in depot form.
- 5 2. Use of an anti-inflammatory steroid by intravitreal injection in depot form for treating macular degeneration.
3. Use according to claim 1 or claim 2, wherein said steroid is in crystalline form.
4. Use according to any one of claims 1 to 3, wherein the steroid is sparingly soluble in the vitreous of the eye.
- 10 5. Use according to any one of claims 1 to 4, wherein the steroid is an 11-substituted 16 α , 17 α -substituted methylenedioxy steroid of the formula:

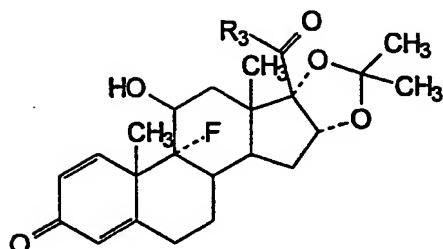


wherein is , , , ,

15 , , , , , or

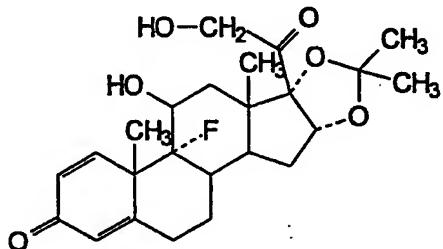
; R₁ and R₂ are hydrogen or alkyl; —Ca—Cb— is —CH₂—CH₂—, —CH₂—CH—, —CH=CH—, —CH=C(CH₃)— or —CH=C(CH₃)—; R₃ is methyl, hydroxymethyl or alkylcarbonyloxymethyl, methylaminoalkylenecarbonyloxymethyl, phenylaminoalkylenecarbonyloxymethyl; R₄ is alkanoyl; and X is halogen.

6. Use according to claim 5, wherein the steroid is



wherein R₃ is hydroxymethyl, phenylcarbonylaminoisopropylcarbonyloxymethyl, or 2,2-dimethylpropylcarbonyloxymethyl.

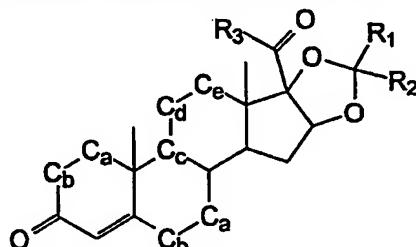
- 5 7. Use according to claim 6, wherein the steroid is 9-fluoro-11,21-dihydroxy-16,17-[1-methylethyldinebis(oxy)]pregna-1,4-diene-3,20-dione:



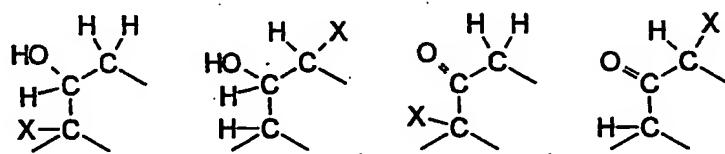
8. Use according to any one of claims 1 to 7, wherein the dosage of steroid is between about 1 and about 8mg.

- 10 9. Use according to claim 8, wherein the dosage is about 4mg.
10. Use according to any one of claims 1 to 9, wherein the macular degeneration is early onset macular degeneration, atrophic macular degeneration or neovascular macular degeneration.
11. Use according to any one of claims 1 to 10, of said steroid in conjunction with 15 a further active substance.
12. Use according to claim 11, wherein the further active substance is an anti-angiogenesis agent.
13. Use according to claim 12, wherein the anti-angiogenesis agent is thalidomide.
14. Use according to claim 11, wherein the further active substance is an 20 antibiotic.
15. Use according to claim 2, or any one of claims 3 to 14 when dependent on a claim other than claim 1, in conjunction with another therapy.
16. Use according to claim 15, wherein the other therapy is laser treatment of the retina and the anti-inflammatory steroid is injected before or after laser treatment.

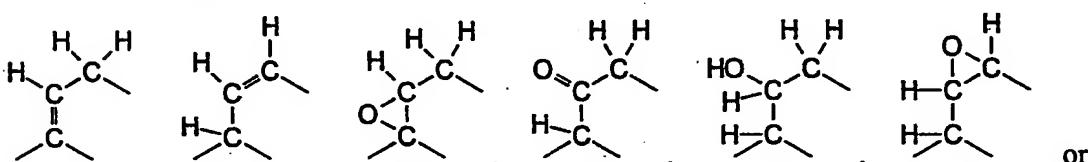
17. A method for the treatment or prophylaxis of macular degeneration in a patient requiring said treatment or prophylaxis, comprising administering by intravitreal injection to said patient an effective amount in depot form of an anti-inflammatory steroid.
 18. The method according to claim 17, wherein the steroid is crystalline.
 - 5 19. The method according to claim 17 or claim 18, wherein the steroid is sparingly soluble in the vitreous of the eye.
 20. The method according to any one of claims 17 to 19, wherein the steroid is an 11-substituted 16 α , 17 α -substituted methylenedioxy steroid of the formula



10 wherein C. is

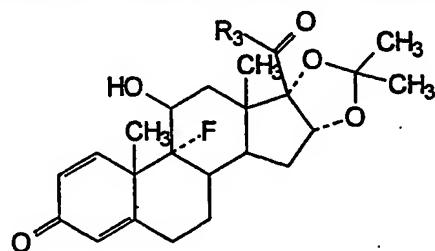


10. Which one of the following is a cyclic compound?



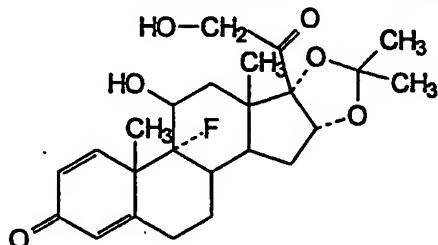
R_1 and R_2 are hydrogen or alkyl; $-\text{C}_a-\text{C}_b-$ is $-\text{CH}_2-\text{CH}_2-$,
 $-\text{CH}_2-\text{CH}-$, $-\text{CH}=\text{C}-$
 $-\text{CH}=\text{CH}-$, CH₃ or CH₃; R_3 is methyl, hydroxymethyl or
 alkylcarbonyloxymethyl, methylaminoalkylenecarbonyloxymethyl, or
 phenylaminoalkylenecarbonyloxymethyl; R_4 is alkanoyl; and X is halogen.

21. The method according to claim 20, wherein the steroid is:



wherein R₃ is hydroxymethyl, phenylcarbonylaminoisopropylcarbonyloxymethyl, or 2,2-dimethylpropylcarbonyloxymethyl.

22. The method according to claim 21, wherein the steroid is 9-fluoro-11,21-dihydroxy-16,17-[1-methylethyldinebis(oxy)]pregna-1,4-diene-3,20-dione:



5

23. The method according to any one of claims 17 to 22 wherein the dosage of steroid is between about 1 and about 8mg.

24. The method according to claim 23 wherein the dosage is about 4mg.

25. The method according to any one of claims 17 to 24 wherein the macular degeneration is early onset macular degeneration, atrophic macular degeneration or neovascular macular degeneration.

26. The method according to any one of claims 17 to 25, comprising a further active substance.

27. The method according to claim 26, wherein the further active substance is an anti-angiogenesis agent.

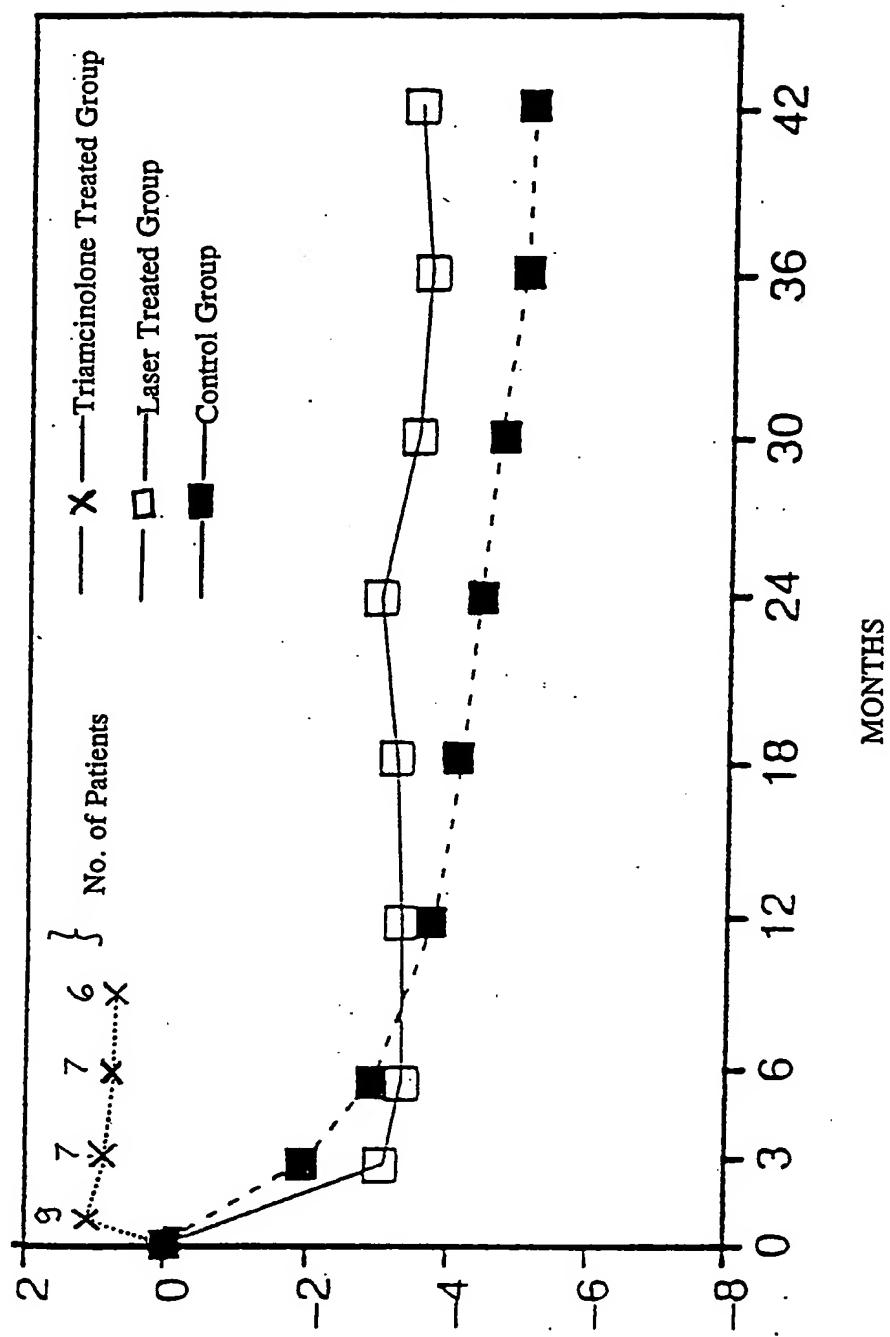
28. The method according to claim 27, wherein the anti-angiogenesis agent is thalidomide.

29. The method according to claim 26, wherein the further active substance is an antibiotic.

30. The method according to any one of claims 17 to 29, wherein the method is practised in conjunction with another therapy.

31. The method according to claim 30, wherein the other therapy is laser treatment of the retina and the anti-inflammatory steroid is injected before or after laser treatment.

1/1



Decrease in Visual Acuity (No. of Lines)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 94/00424

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.⁵ A61K 31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/57Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as aboveElectronic data base consulted during the international search (name of data base, and where practicable, search terms used)
WPAT, CASM, A61K: TRIAMCINOLONE ACETONIDE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Patent Abstracts of Japan, C-1181, page 52, JP,A,5-331050 (POLA CHEM IND INC) 14 December 1993 (14.12.93)	1-16
X	AU 16150/83 (SHIONOGI & CO LTD) 5 January 1984 (05.01.84) whole document	1-16
X	US 3962430 (O'NEILL) 8 June 1976 (08.06.76) whole document, column 7, example 11	1-31
X	US 3758686 (SIEGER et al) 11 September 1973 (11.09.73) whole document, column 4, example 5	1-31

 Further documents are listed
in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search
6 October 1994 (06.10.94)Date of mailing of the international search report
8 Nov 1994 (8.11.94)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 94/00424

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
X	Antoszyk A.N. et al, Graefe's Arch Clin Exp Ophthalmol (1993) 231, 34-40	1-31
X	Ishibashi et al, Arch Ophthalmol (1985) 103, 708	1-31

INTERNATIONAL SEARCH REPORT

Information on patent family member:

International application No.

PCT/AU 94/00424

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document
Cited in Search
Report

Patent Family Member

AU	16150/83	EP	97374	GB	8317099	GB	2122087
JP		JP	58225009				
US	3962430	DE	1617628				
US	3758686						
JP	5331050						

END OF ANNEX